

WHAT IS CLAIMED IS:

1. A method for detecting proteolysis of an LDL receptor transmembrane domain, comprising the steps of:

5 a) providing a sample comprising a cell membrane comprising (i) a polypeptide comprising an LDL receptor transmembrane domain fused to a C-terminal tail, and (ii) a protease which specifically cleaves the domain and thereby releases the tail from the membrane;

b) incubating the sample under conditions wherein the protease cleaves the domain and thereby releases the tail from the membrane; and

10 c) detecting a resultant released tail.

2. A method according to claim 1, wherein the sample comprises a viable cell which comprises the membrane.

15 3. A method according to claim 1, wherein the sample comprises a viable cell which comprises the membrane, the tail comprises an intracellular transcription factor domain, the cell further comprises a transcriptional reporter responsive to release of the transcription factor domain from the membrane, and the detecting step comprises detecting expression of the reporter as an indication of the released tail.

20 4. A method according to claim 1, wherein the sample comprises a cellular membrane extract which comprises the membrane.

25 5. A method according to claim 1, wherein the sample comprises a cellular membrane extract which comprises the membrane, and the detecting step comprises selectively detecting released, soluble tails.

30 6. A method according to claim 1, wherein the sample comprises a cellular membrane extract which comprises the membrane, and the detecting step comprises selectively detecting released, soluble tails by solid-phase affinity adsorption assay.

7. A method according to claim 1, wherein the tail comprises an affinity tag.

35 8. A method according to claim 1, wherein the tail comprises at least a portion of the cytoplasmic domain of the LDL receptor.

9. A method according to claim 1, wherein the protease is native to the membrane.

10. A method according to claim 1, wherein the protease is gamma secretase.

11. A method according to claim 1, wherein the LDL receptor is selected from the group consisting of LRP, LRP1b, megalin, LDLR, VLDLR, ApoER2, MEGF7, LRP5, LRP6 and LR11.

12. A method according to claim 1, wherein the LDL receptor is LRP and the protease is native to the membrane.

13. A method according to claim 3, wherein the LDL receptor is LRP and the protease is native to the membrane.

14. A method according to claim 5, wherein the LDL receptor is LRP and the protease is native to the membrane.

15. A method according to claim 1, wherein the LDL receptor is LRP1b and the protease is native to the membrane.

16. A method according to claim 3, wherein the LDL receptor is LRP1b and the protease is native to the membrane.

17. A method according to claim 5, wherein the LDL receptor is LRP1b and the protease is native to the membrane.

18. A method according to claim 1, wherein the LDL receptor is megalin and the protease is native to the membrane.

19. A method according to claim 3, wherein the LDL receptor is megalin and the protease is native to the membrane.

20. A method according to claim 5, wherein the LDL receptor is megalin and the protease is native to the membrane.